

Original article

Association of synaptosomal-associated protein 25 (SNAP-25) gene polymorphism with temperament and character traits in women with fibromyalgia syndrome

ATALAY DOGRU¹, AYSE BALKARLI², EMRE TEPELI³, EMEL AYDIN⁴, VELI COBANKARA⁵

¹ Dr. Ersin Arslan Training and Research Hospital, Department of Internal Medicine, Division of Rheumatology, Gaziantep, Turkey.

² Antalya Training and Research Hospital, Department of Internal Medicine, Division of Rheumatology, Antalya, Turkey.

³ Pamukkale University, Department of Medical Biology, Denizli, Turkey.

⁴ Pamukkale University, Department of Psychiatry, Denizli, Turkey.

⁵ Pamukkale University, Department of Internal Medicine, Division of Rheumatology, Denizli, Turkey.

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Abstract

Background: Synaptosomal-associated protein 25 (SNAP-25) may contribute to the pathogenesis of fibromyalgia Syndrome (FMS) by affecting the release of neurotransmitters. **Objectives:** We aimed to investigate the relationship between the SNAP-25 gen (*DdeI* = rs1051312 and *MnII* = rs3746544) polymorphism and the temperament and character traits. **Methods:** A total of 85 female patients diagnosed with FMS and 70 age-matched healthy female subjects were enrolled into the study. The Temperament and Character Inventory (TCI) were performed on all the patients. SNAP-25 gene polymorphism was determined in the patients group and controls group. **Results:** No significant difference between groups was found regarding the distribution of SNAP-25 *MnII* polymorphism ($p > 0.05$), but it was seen that the frequency of TC genotype for *DdeI* gene was higher in the patients group ($p < 0.05$). Increased hazard avoidance was found in the patients group ($p < 0.05$). When TCI scores were assessed in terms of SNAP-25 gene polymorphism, no statistically significant relationship was detected between the TT, TG, GG genotypes for *MnII* gen and TCI scores ($p > 0.05$). However, increased hazard avoidance was detected in patients with TC genotype for *DdeI* gene compared to patients without such genotype. **Discussion:** SNAP-25 might be an etiological factor in FMS pathogenesis and might affect personality traits of FMS patients by mediating neurotransmitter release.

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Keywords: Fibromyalgia syndrome, SNAP-25 gene polymorphism, temperament and character inventory.

Introduction

Fibromyalgia syndrome (FMS) is a common chronic musculoskeletal disorder characterized with widespread pain and multiple sensitive points in physical examinations, the etiology of which is not completely known. It is a syndrome accompanied by many systemic disorders. Although it is an illness which can be seen in every age group, its frequency increases with age. It is most common between the ages 20 and 55. It is mostly seen in women¹.

Co-diagnosis of psychiatric disorders in FMS is common. When previous studies are considered, the most common psychiatric disorders that coexist with FMS are depression, somatization disorder, bipolar disorder, anxiety and obsessive compulsive disorder^{2,3}. Assuming that some personality and temperament traits may predispose to FMS, character evaluation studies have been conducted, and various disorders have been found in personality inventory profiles⁴. Although symptoms that involve many systems can be seen, the symptom that bothers patients most is widespread pain. Unfortunately, there is no effective treatment of FMS. This is an important problem not only for patients, but also for clinicians. Therefore, studies for etiopathogenesis usually target the enlightenment of pathogenesis of pain. While the etiology and mechanisms of FMS are still not thoroughly understood, however, pain mechanisms and central sensitization in addition to neuroendocrine dysfunctions seem to be the most important factors in occurrence of FMS. Many factors can trigger or modulate neuroendocrine anomalies in FMS. Because psychiatric disorders frequently accompany to FMS, studies performed to enlighten its etiopathogenesis usually focus on psychiatric disorders and pain mechanisms⁵. As known, serotonin and dopamine are the neurotransmitters, the roles of which have been widely discussed in the etiology of depression and anxiety disorders. Recent studies

have found that levels of serotonin, noradrenalin and dopamine are distinctly low in FMS patients⁶.

SNARE (soluble N-ethylmaleimide-sensitive factor activating protein receptor) proteins are proteins that have basic role in fusion between eukaryotic cells and organelles, and between organelles and plasma membrane⁷. Synaptosomal-associated protein 25 (SNAP-25) is a SNARE protein found in plasma membrane. These proteins play a very important role in regulation of voltage-gated calcium channels and transmission of neurotransmitters between nerve cells. Neurotransmitters are found in synaptic vesicles, and are sent to the other synapse by way of exocytose⁸. It is essential for normal brain functions. Several studies have reported that abnormalities in structure and expression of SNAP-25 are associated with various neurological disorders^{9,10}. For this reason, SNAP-25 may be contributing to the pathogenesis of FMS by mediating the release of neurotransmitters such as serotonin and dopamine. In a study carried out by Balkarli *et al.*¹¹ which was the preliminary of our study, it was reported that SNAP-25 gene polymorphism was more frequently detected in FMS. Depression and pain score was higher in patients with *DdeI* T/C genotype. Therefore, we intend to investigate the relationship between SNAP-25 gen (*DdeI* = rs1051312 and *MnII* = rs3746544) polymorphism and the temperament and character traits.

Methods

Patients and evaluation

A total of 85 female patients diagnosed with FMS according to the ACR 2010 FMS diagnostic criteria, and 70 age-matched healthy female subjects were enrolled in the study. Postmenopausal or climacteric female patients were not enrolled in the study. Here, the objective was to reduce the effect of hormonal changes, and to reduce



the effect of osteoporosis which usually accompanies to FMS in the postmenopausal period. Because depression affects personality and temperament traits, all the patients were evaluated with the Beck depression inventory (BDI) during the screening phase. The patients, whose BDI scores were ≥ 11 , were excluded from the study. We tried to minimize the contribution of depression to personality traits. In order to obtain accurate data about the symptoms of the patients, subjects graduated at least from 8th class or attending 8th class were enrolled to the study, since more educated patients explain their symptoms better. All patients and healthy subjects were informed on the study. After informed consents from the patients group and controls were obtained, their blood samples were collected into 10 cc EDTA tubes, and were kept at -20°C . Genetic analyses were performed on the samples in the Medical Genetics Department. The Temperament and Character Inventory (TCI) consisting of 240 questions was performed and assessed on both groups. Approval of the local ethics committee was obtained for the study.

Tools

Socio-demographic Information Form

This form was developed by the investigators, and data such as age, gender, educational background, socioeconomic status, place of residence, marital status and duration of illness were recorded on the form.

BDI

This inventory was used to determine the depression risk of subjects, and to measure the changes in level and severity of depressive symptoms. It was developed by Beck *et al.*, and the studies for validation, reliability testing and adaptation of it into Turkish were conducted by Hisli¹².

TCI

It is a self-report inventory that evaluates four temperament and three character traits, which is filled out as "wrong/correct", which consists of 240 items, which can be completed in 30-45 minutes, and which can be applied to people 17 and above years old. All dimensions except for the persistence were divided into three and five subscales. In the temperament dimension, novelty seeking (NS) was divided into 4 subscales (NS1: exploratory excitability, NS2: impulsiveness, NS3: extravagance, NS4: disorderliness); and harm avoidance (HA) was divided into 4 subscales (HA1: anticipatory worry, HA2: fear of uncertainty, HA3: shyness, HA4: fatigability); and reward dependence (RD) was divided into 3 subscales (RD1: sentimentality, RD3: attachment, RD4: dependence). In the character dimension, self-directedness (SD) was divided into 5 subscales (SD1: responsibility, SD2: purposefulness, SD3: resourcefulness, SD4: self-acceptance, SD5: enlightened second nature); and cooperativeness (C) was divided into 5 subscales (C1: social acceptance, C2: empathy, C3: helpfulness, C4: compassion, C5: pure-hearted conscience); and self-transcendence (ST) was divided into 3 subscales (ST1: self-forgetfulness, ST2: transpersonal identification, ST3: spiritual acceptance)¹³.

Molecular analysis

Genetic analyses were performed at the Medical Genetics Department. Genomic DNAs of the patients and the controls were isolated from peripheral blood by using QuickGene DNA whole blood kit (Kurabo, Japan). In order to multiply the UTR region of the 8th exon, where the *DdeI* (rs1051312) and *MnII* (rs3746544) polymorphisms of the SNAP-25 gene are found, the primary sequences predefined in the literature as forward 5'- TTC TCC TCC AAA TGC TGT CG-3' and reverse 5'- CCA CCG AGG AGA GAA AAT G-3' were used.

In the PCR reaction, which was formed by using these primary sequences, 10X PCR Buffer, 5 μl dNTP mixture containing 0,2 mM of every nucleotide, and Taq polymerase enzyme were also used. The PCR reaction conditions performed: After the first 2-minute denaturation at 95°C , following 35 cycles consisting of 1 minute at 58°C and 2 minutes at 72°C , a final extension of 7 minutes at 72°C .

10 U *DdeI* and 10 U *MnII* enzymes were separately added to the PCR products of 261 base pairs obtained, and they were left to fragmentation at 37°C for 14 hours. For separation of the fragments that were formed after fragmentation, 3.5% ultra-pure agarose gel was prepared. Then, the PCR products were subjected to gel electrophoresis for 40-50 minutes, and divided into fragments. The allele band sequencings expected for *DdeI* polymorphism after electrophoresis for the T allele: an uncut band of 261 base pairs; for the C allele: two separate bands of 228 base pairs and 33 base pairs. The allele band sequencings expected for *MnII* polymorphism for the T allele: two separate bands of 256 base pairs and 5 pairs, for the G allele: three separate bands of 210 base pairs, 46 base pairs and 5 base pairs.

Statistical analysis

Statistical package for the Social Sciences (SPSS) (IBM Corp, Armonk, New York, USA) 20.0 software was used for statistical evaluation. Descriptive statistics included mean, standard deviation and percentage. The confidence interval of the study was determined as 95%. First of all, Kolmogorov-Smirnov normality test was conducted for analysis of the differences between the ages, number of births, and number of children of the patients group and the controls group. At the end of the normality test, it was decided to use Mann-Whitney U test for the nonparametric tests. For analysis of marital status of the patients group and control group, Fischer's exact test was used. For analysis of the differences between the patients group and the controls group in terms of the places they live in, occupational status, and *MnII*, *DdeI* genes; Pearson chi-square test was used. Allele frequencies were calculated with the Hardy-Weinberg equation. p , q : allele frequency, p^2 , q^2 , $2pq$: genotype frequency. $p+q=1$

$$(p^2)+(2pq)+(q^2)=1$$

Spearman correlation analysis was used to identify associations between the parameters. $p < 0.05$ was considered statistically significant.

Results

Of the patients, the mean age was 41.2 ± 5.3 years, and the mean durations of the symptoms was 7.43 ± 1.9 years, and the mean level of hemoglobin was 12.97 ± 0.81 g/dL. Eighty one (95.2%) patients were married, and 4 (4.8%) patients were single. Sixty two (72.9%) patients lived in the city, and 23 (23%) patients lived in the country. Twenty eight (32.9%) patients were working, and 57 (67.1%) patients were unemployed. The patients group and the controls group were similar with regards to their ages, marital status, the places they live in and occupational status.

When the *MnII* (rs3746544) gene polymorphism distribution in the patients group and the controls group were reviewed, there were 38 subjects (44.70%) with TT genotype, 39 subjects (45.88%) with TG genotype, and 8 subjects (9.41%) with GG genotype. In the control group, there were 32 subjects (45.71%) with TT genotype, 23 subjects (32.86%) with TG genotype, and 15 subjects (21.42%) with GG genotype. When the *DdeI* (rs1051312) genotype distribution was reviewed, there were 35 subjects (41.1%) with TT genotype, 47 subjects (55.2%) with TC genotype, and 3 subjects (3.5%) with CC genotype in the patients group. In the control group, there were 46 subjects (65.7%) with TT genotype, 19 subjects (27.1%) with TC genotype, and 5 subjects (7.1%) with CC genotype. No difference between the groups was found regarding the distribution of SNAP-25 *MnII* polymorphism, but statistically significant difference was found

between the groups with regards to *DdeI* polymorphism ($p = 0.004$). When a separate matchings review was done to find out the source of the difference, it was seen that the difference was caused by the higher number of TC genotype in the patients group. No difference was found between the two groups with regards to allele frequency (Table 1).

When the TCI scores of the patients group and controls were compared, NS, NS4 and RD4 scores of the patients were found lower than those of the control group (p values 0.002, < 0.001 , < 0.001 respectively), and HA, HA1, HA2, HA4, S5 scores were found higher in the patients compared to controls ($p < 0.05$), (Table 2).

Table 1. SNAP-25 gene allele and genotype distribution in the patients group and controls group

	Patients n, %	Controls n, %	p
Mnl1 gene genotype/allele			
TT	38 (44.70%)	32 (45.71%)	0.248
TG	39 (45.88%)	23 (32.86%)	
GG	8 (9.41%)	15 (21.42%)	
T allele	115 (67.6%)	87 (62.14%)	0.500 (Pearson chi-square) Odds ratio 1.193 (95% CI 0.714-1.995)
G allele	55 (32.4%)	53 (38.85%)	
	HWE $p = 0.718$	HWE $p = 0.037$	
Ddel gene			
TT	35 (41.1%)	46 (65.7%)	0.004
TC	47 (55.2%)	19 (27.1%)	
CC	3 (3.5%)	5 (7.1%)	
T allele	117 (68.82%)	111 (79.28%)	0.089 (Pearson chi-square) Odds ratio 1.62 (95% CI 0.926-2.849)
C allele	53 (31.17%)	29 (20.71%)	
	HWE $p = 0.004$	HWE $p = 0.330$	

SNAP 25: Synaptosomal-associated protein 25, HWE: Hardy-Weinberg equation.

Table 2. TCI values of Patients Group and Control Group

TCI parameter	Patients n = 85	Controls n = 70	P
NS	15.73 \pm 4.78	18.16 \pm 4.780	0.002
NS1	5.38 \pm 2.17	5.67 \pm 1.835	0.299
NS2	4.88 \pm 7.06	4.05 \pm 2.125	0.998
NS3	3.46 \pm 1.586	3.46 \pm 1.908	0.115
NS4	2.64 \pm 1.445	4.47 \pm 1.872	< 0.001
HA	20.48 \pm 6.81	16.63 \pm 5.811	< 0.001
HA1	6.62 \pm 1.769	5.58 \pm 2.095	0.003
HA2	4.25 \pm 1.796	3.37 \pm 1.665	0.003
HA3	3.98 \pm 2.569	3.98 \pm 2.569	0.441
HA4	5.46 \pm 2.181	3.89 \pm 2.177	< 0.001
RD	13.14 \pm 2.954	14.23 \pm 3.123	0.71
RD1	7.32 \pm 1.53	7.16 \pm 1.73	0.546
RD3	3.76 \pm 1.549	4.19 \pm 1.586	0.065
RD4	1.94 \pm 1.165	2.88 \pm 1.196	< 0.001
P	5.29 \pm 1.541	5.19 \pm 2.057	0.883
SD	26.05 \pm 7.669	25.02 \pm 6.86	0.227
SD1	3.98 \pm 2.43	3.95 \pm 2.191	0.917
SD2	5.42 \pm 2.213	5.04 \pm 1.70	0.099
SD3	2.81 \pm 1.66	3.21 \pm 1.436	0.144
SD4	5.2 \pm 2.75	5.6 \pm 2.243	0.315
SD5	8.94 \pm 2.62	7.23 \pm 2.291	< 0.001
C	26 \pm 6.684	25.46 \pm 6.459	0.373
C1	5.54 \pm 1.793	5.49 \pm 1.872	0.800
C2	3.8 \pm 1.471	4.11 \pm 1.472	0.401
C3	4.32 \pm 1.592	4.44 \pm 1.376	0.738
C4	6.51 \pm 1.892	6.07 \pm 2.034	0.170
C5	5.74 \pm 1.729	5.28 \pm 1.677	0.067
ST	18.2 \pm 4.64	19.32 \pm 4.958	0.176
ST1	5.68 \pm 2.196	6.09 \pm 2.081	0.350
ST2	5.10 \pm 1.74	5.11 \pm 2.102	0.701
ST3	7.43 \pm 1.941	8.12 \pm 2.376	0.410

TCI: Character and Temperament Inventory; NS: novelty seeking; HA: harm avoidance; RD: reward dependence; P: persistence; SD: self-directedness; C: cooperativeness; ST: self-transcendence.

Values are presented as mean \pm standard deviation.

$p < 0.05$ is significant; NS: non significant.

When the TCI scores were assessed in terms of the types of SNAP-25 gene polymorphism, no statistically significant relationship between TT, TG, GG genotypes for the *MnII* gen and TCI scales was detected ($p > 0.05$). However, NS, NS4 score was found lower in the patients with TC genotype for *DdeI* gene ($p < 0.05$, Table 3), and HA, HA1, HA2 and C5 scores were found higher ($p < 0.05$). No statistically significant difference was found between TCI scores of the patients with and without C allele, although we assume the difference to be clinically significant. We found that NS and ST3 were significantly low, whereas; HA, HA1, HA2 and C5 were significantly high ($p < 0.05$), (Table 3).

Discussion

The etiology of FMS is still unknown, but it seems to be multifactorial. FMS is classified as a functional somatic syndrome. Co-diagnosis of psychiatric disorders in FMS is common. In previous studies; depression, somatization disorder, bipolar disorder, anxiety and obsessive compulsive disorder have been found to be the most common coexisting disorders with FMS^{2,3}. Cloninger *et al.* have found in their study that patients with chronic pains have higher HA, lower C and lower SD scores compared to healthy controls group¹³. It is assumed that personality also plays an important role in the etiology of psychosomatic illnesses. It is stated that there are specific personality traits for each psychosomatic illness¹⁴.

Temperament is a tendency to react automatically against emotional stimulations in a naturally structurally certain way. Character is, on the other hand, relatively unchanging objectively observable behaviors, and subjectively stated internal experiences. Cloninger developed a dimensional psychobiological model of personality that accounted for both normal and abnormal variations of two major components of personality¹³. Cloninger's personality model includes four temperaments (NS, HA, RD and persistence), and three character dimensions (SD, C and ST). There is limited research on character and temperament of FMS patients. The common finding of these studies is high scores of HA^{4,15-17}. We also found higher HA in FMS patients compared to the healthy controls group in our study. It has been shown in studies that high HA is associated with severity somatization¹⁸.

The findings we obtained from our study show that there are some differences in the personality traits and sub-dimensions of FMS patients compared to controls. Our study has found increased HA and decreased NS in FMS patients. There is limited research on character and temperament of FMS patients. However, only two of these studies used the TCI developed by Cloninger. The common finding of these studies is high scores of HA. These two studies conducted with TCI have reported high scores of HA and low scores of SD in FMS patients^{16,17}. Conrad *et al.*¹⁹ found high HA and low SD scores in patients with chronic pains. Patients diagnosed with depression were also included in these studies, and a positive correlation has been

Table 3. TCI scores of Patients Group and Control Group based on genotypes and alleles

TCI Parameter	TC Genotype (+) patients n = 47	TC Genotype (-) patients n = 38	p	C allele (+) patients	C allele (-) patients	p
NS	14.84 ± 4.066	16.61 ± 4.753	0.042	14.72 ± 3.99	16.85 ± 4.78	0.025
NS1	5.41 ± 1.81	5.47 ± 2.58	0.898	5.44 ± 1.78	5.44 ± 2.64	0.992
NS2	3.81 ± 1.898	6.19 ± 10.436	0.176	3.77 ± 1.87	4.62 ± 1.97	0.062
NS3	3.3 ± 1.525	3.53 ± 1.52	0.520	3.18 ± 1.57	3.68 ± 1.43	0.162
NS4	2.27 ± 1.217	2.97 ± 1.5	0.031	2.28 ± 1.19	3.00 ± 1.53	0.035
HA	22.11 ± 6.244	18.64 ± 7.68	0.038	21.77 ± 6.48	18.82 ± 7.65	0.040
HA1	7.08 ± 1.6	6.19 ± 1.939	0.037	7.05 ± 1.66	6.18 ± 1.89	0.048
HA2	4.89 ± 1.449	3.5 ± 1.905	0.001	4.79 ± 1.47	3.53 ± 1.95	0.003
HA3	4.49 ± 2.388	3.19 ± 2.776	0.056	4.38 ± 2.43	3.24 ± 2.78	0.111
HA4	5.46 ± 2.317	5.56 ± 2.223	0.857	5.36 ± 2.36	5.68 ± 2.14	0.521
RD	12.95 ± 2.613	13.36 ± 3.339	0.555	12.85 ± 2.62	13.50 ± 3.35	0.362
RD1	7.3 ± 1.45	7.44 ± 1.681	0.690	7.23 ± 1.45	7.53 ± 1.67	0.404
RD3	3.57 ± 1.345	3.83 ± 1.444	0.418	3.54 ± 1.31	3.88 ± 1.47	0.386
RD4	2.08 ± 1.09	1.81 ± 1.238	0.316	2.08 ± 1.08	1.79 ± 1.25	0.214
P	5.54 ± 1.574	5.19 ± 1.489	0.338	5.56 ± 1.55	5.15 ± 1.50	0.133
SD	25.43 ± 6.743	25.5 ± 8.484	0.970	25.87 ± 6.85	25.00 ± 8.45	0.628
SD1	3.81 ± 2.158	4 ± 2.64	0.738	3.85 ± 2.13	3.97 ± 2.69	0.858
SD2	5.22 ± 2.275	5.56 ± 2.298	0.528	5.31 ± 2.26	5.47 ± 2.32	0.542
SD3	2.57 ± 1.537	2.83 ± 1.92	0.515	2.69 ± 1.59	2.71 ± 1.89	0.826
SD4	5.05 ± 2.677	4.86 ± 2.779	0.763	5.18 ± 2.66	4.71 ± 2.78	0.332
SD5	8.78 ± 1.315	8.94 ± 3.641	0.802	8.85 ± 1.30	8.29 ± 1.60	0.110
C	26.54 ± 6.09	25.39 ± 7.762	0.483	26.64 ± 5.98	25.21 ± 7.93	0.314
C1	5.54 ± 1.865	5.56 ± 1.843	0.973	5.56 ± 1.81	5.53 ± 1.89	0.864
C2	3.84 ± 1.385	3.86 ± 1.676	0.949	3.87 ± 1.39	3.82 ± 1.67	0.669
C3	4.14 ± 1.601	4.39 ± 1.695	0.513	4.13 ± 1.62	4.41 ± 1.67	0.812
C4	6.73 ± 2.023	6.39 ± 1.917	0.463	6.74 ± 1.98	6.35 ± 1.95	0.301
C5	6.05 ± 1.508	5.22 ± 1.987	0.047	6.10 ± 1.48	5.12 ± 1.99	0.025
ST	18.41 ± 4.862	18.67 ± 4.641	0.815	18.31 ± 4.78	18.79 ± 4.70	0.739
ST1	6 ± 2.273	5.64 ± 2.27	0.499	5.90 ± 2.26	5.74 ± 2.28	0.750
ST2	5.3 ± 1.762	5.17 ± 1.699	0.748	5.33 ± 1.78	5.12 ± 1.66	0.593
ST3	7.05 ± 1.747	7.92 ± 2.089	0.059	7.03 ± 1.73	8.00 ± 2.08	0.029

TCI: Character and Temperament Inventory; NS: novelty seeking; HA: harm avoidance; RD: reward dependence; P: persistence; SD: self-directedness; C: cooperativeness; ST: self-transcendence.

Values are presented as mean ± standard deviation.

$p < 0.05$ is significant; NS: non significant.

found between low SD scores and depression scores^{16,17}. It has been reported that there is an increase in HA scores and decrease in SD scores in emotional pathologies associated with depressive state^{20,21}. Considering the likelihood of depression, we screened our patients with BDI and did not include the patients whom we found to have BDI scores higher than 17 in the study. Thus, we minimized the effect of depression on character and temperament. Therefore, SD score in FMS patients may have found to be normal, unlike in other studies.

Patients with high HA behavior are defined as careful, meticulous, passive, fearful and insecure. Similar findings have been found in all these studies including our study, suggesting that these personality traits cause more susceptibility to developing mood and pain disorders.

One of the hypotheses emphasized with respect to FMS etiopathogenesis is the serotonin (5-hydroxytryptamine) hypothesis²². Serotonin is found both in peripheral and in central serotonergic neurons. As known, serotonin and dopamine are the neurotransmitters, the roles of which have been widely discussed in the development of pain and etiology of depression and anxiety disorders. Serum levels of tryptophan, which is the precursor of serotonin, have been found to be low in patients with FMS²³. In another study, decrease has been detected in 5-hydroxyindoleacetic acid levels, which is the serotonin metabolite, in cerebrospinal fluid of FMS patients²⁴.

SNARE proteins are proteins that have basic role in fusion between eukaryotic cells and organelles, and between organelles and plasma membrane⁷. SNAP-25 is a SNARE protein found in plasma membrane. These proteins play a very important role in formation of protein receptor complex which are responsible for the transmission of neurotransmitters between nerve cells. Neurotransmitters are found in synaptic vesicles and released at the synapse by way of calcium-dependent exocytosis⁸. For this reason, SNAP-25 is important in the release of neurotransmitters such as serotonin and dopamine. Changes in the SNAP-25 functions may cause changes in the levels of serotonin and other neurotransmitters. Cloninger's personality model makes it possible to correlate behavior appearances with neurotransmitters. In a study carried out by Peirson and Heuchert²⁵, it was reported that HA tendency is linked to serotonin activation, and there is a negative correlation between serotonergic activation and HA tendency of the individuals. Individuals with high HA respond to stressful events with high levels of depressive signs. These individuals expect danger even when there is no danger^{13,26}. This expectation leads to an inappropriate adaptation. Such individuals may have the tendency to wait for the pain to begin. No common personality profile has been established for psychosomatic illnesses. However, the common result is that the HA scores are high. Cloninger described that people with chronic anxiety difficultly calm down, get tired easily, and display specific signs based on specific anticipatory anxiety²⁷. The high scores of HA, which we found in FMS patients, suggest that these patients may have a temperament with a tendency to develop pain symptoms as a response to stress.

In a study of Balkarli *et al.*¹¹, it was found that SNAP-25 gene polymorphism was more frequently detected in FMS. Depression and pain score was higher in patients with DdeI T/C genotype. In our study, we also found lower NS, lower NS4, higher HA, high HA1, high HA2, and high C5 in the patients with this genotype. We compared the TCI scores of patients with and without C allele, and we found difference in their TCI parameters ($p < 0.005$, Table 3).

There is limited research on character and temperament of FMS patients¹⁵⁻¹⁷. Different inventories have been used in these studies. Personality models other than TCI have not taken into account the underlying social and biological identifiers, have failed in distinguishing types of memory. Cloninger's psychobiological personality model (TCI) evaluates the responses of a person to novelty, danger and various types of reward with four basic personality dimensions. This way, it has been determined that basic emotions mediate perceptive information processes, and form early learning patterns such as unconscious responses to conditioned stimuli, and inherited tendencies of information processed by memory systems have been reflected¹³. Using the TCI to evaluate

character and temperament in our study is supremacy of our study. Furthermore, most of these patients are also diagnosed with depression. Yet, higher HA, lower SD and lower persistence have been found in subjects with depression compared to healthy individuals. It has been reported that these personality traits may also be related to the severity of depressive symptomatology²⁸⁻³⁰. For this reason, we did not include patients with depression into our study. Therefore, we minimized the contribution of depression to personality traits. This is the supremacy of our study.

Our study had various restrictions. First of all, the number of patients was limited, and we tried to explain pathology with only one gene. Serotonin and dopamine levels were not measured. The use of BDI instead of Structured clinical interview for DMS-IV diagnosis for the diagnosis of depression was another limitation. The fact that there was no psychiatric evaluation or screening test for other common diseases (such as bipolar disorder) was another shortcoming of this study. Although it was stated that patients with higher educational background were included in order to fill these form more accurately, level of education may an effect on severity of disease symptoms and temperament.

In conclusion, SNAP-25 might be an etiological factor in FMS pathogenesis and might affect personality traits of FMS patients by mediating neurotransmitter release. The findings of our study may be considered as preliminary data, and further studies are required to be conducted. We think that studies with larger patient populations, in which serotonin and serotonin receptors will also be evaluated, will be beneficial for enlightening of the subject matter.

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Conflict of interest

No conflict of interest was declared by the authors.

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